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GSK Medicine: Diclofenac diethylammonium
Study Number: A2620383
Title: A Proof of Principle Study to Investigate the Efficacy of a Medical Device and Topical Analgesic Combination for the Treatment of Pain and Performance Related Function in Osteoarthritis
Rationale: To determine whether the combination of topical diclofenac and a heat patch is more effective than the standard treatment topical diclofenac alone.
Phase: Not applicable
Study Period: 5th February 2008 to 12th June 2008
Study Design: This was a proof of principle single centre study, single (assessor) blind, randomised, three way crossover, in subjects with osteoarthritis (OA) of the knee. Following a Screening Visit, eligible subjects underwent a washout period from their current OA medication of 7-14 days prior to the first Baseline Visit. All three treatment periods consisted of a Baseline Visit and a post-treatment visit which were separated by exactly 72 hours (hrs) of treatment. For each treatment period subjects applied the treatment two times a day for 72 hrs, each treatment application remained on the knee for approximately 8 hrs. There was a 7-10 day washout period between each treatment period. Subjects were provided with rescue medication (standard paracetamol) for use, if required, during the treatment and washout periods. Subjects completed the Western Ontario and McMasters University (WOMAC) osteoarthritis index at all visits. The subject's pain, stiffness and difficulty to perform various activities were rated by subjects as per the WOMAC scale which is based on questionnaire. The responses were based on a 5-point Likert scale as detailed below: 0=None; 1=Mild; 2= Moderate; 3=Severe; 4=Extreme. Measurement of time to walk 20 meter (m), time to walk 40 m, stair climbing and subjective assessments of pain were made at all baseline and post-treatment visits. The subjects indicated their pain at that time using a pain rating scale. The pain rating was based on a 5-point Likert scale: 0 = None; 1 = Mild pain; 2 = Moderate pain; 3 = Severe pain; 4 = Extreme pain. A single plasma sample to determine diclofenac level was obtained at all post-treatment visits.
Centre: 1 in United Kingdom
Indication: Pain
Treatments: Test Product: Diclofenac gel (4 g of gel containing 1.16% diclofenac diethylammonium) with a heat patch
Reference Products: 1. Diclofenac gel (4 g of gel containing 1.16% diclofenac diethylammonium) with a placebo heat patch (expelled of heat) 2. Placebo gel (4 g of gel) applied topically to the knee and covered with a heat patch
Objectives: Primary Objective: To compare the efficacy of 72 hrs treatment with topical diclofenac plus a heat patch to 72 hrs treatment with topical diclofenac plus a placebo patch on time to climb stairs and on pain following stair climbing Secondary Objectives: 1. To compare the efficacy of 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of placebo gel plus a heat patch on time to climb stairs and on pain following stair climbing. 2. To compare the efficacy of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch on the following secondary endpoints: <ul style="list-style-type: none"> • Time to walk 20 m; • Time to walk 40 m; • Pain following walking 40 m; • Pain at rest; • WOMAC scores; • Mean consumption of rescue medication based on consumption per patient per treatment.

Primary Outcome Endpoints:	
<ol style="list-style-type: none"> 1. Time to climb stairs on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of topical diclofenac plus a placebo patch 2. Pain following stair climbing on 72 hours hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of topical diclofenac plus a placebo patch 	
Secondary Outcome Endpoints:	
<ol style="list-style-type: none"> 1. Time to climb stairs on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of placebo gel plus a heat patch 2. Pain following stair climbing on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of placebo gel plus a heat patch 3. Time to walk 20 m on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch 4. Time to walk 40 m on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch 5. Pain following walking 40 m on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch 6. Pain at rest on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch 7. WOMAC scores on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch: 8. Mean consumption of rescue medication based on consumption per patient per treatment on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch 	
Statistical Methods:	
<p>The primary efficacy analysis was a mixed model analysis of variance on time to climb stairs, followed by a multiple comparison t-test to compare topical diclofenac gel plus heat patch to topical diclofenac gel plus placebo patch. The fixed effects in the model were treatment and period; patient was a random effect. The multiple comparison t-tests were 2-sided, conducted at the 5% significance level. The same analysis was performed on the endpoint of pain following stair climbing. In the secondary efficacy analysis, another multiple comparison t-test was performed following the analysis of variance (ANOVAs) in the primary analysis, to compare topical diclofenac gel plus heat patch to placebo gel plus heat patch. The secondary parameters listed above were each analysed using the same model as in the primary analysis but the multiple comparisons following the ANOVA was a Dunnett's Test comparing topical diclofenac gel plus heat patch to each of topical diclofenac gel plus placebo patch and placebo gel plus heat patch.</p>	
Study Population:	
Subject Disposition	
	Overall
Subjects Randomized, n	69
Subjects completed study, n	63
Subject did not complete the study, n	6
Reason for not completing the study, n	
Adverse Event	0
Lost To Follow-Up	0
Protocol Deviation	2
Withdrawal Of Consent	0
Other	4
Demographics (All Randomized Subjects)	
	Overall
N	69
Sex, n (%)	
Male: Female	45 (65.2): 24 (34.8)
Mean Age, years (SD)	67.59 (6.779)
Race, n (%)	
Caucasian	68 (98.6)
Black	1 (1.4)
Primary Outcome Results (Intent to Treat [ITT] population N=69):	

Table 1: Time to climb stairs (seconds) on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of topical diclofenac plus a placebo patch

Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch
n	68	65
Mean (SD)	26.82 (11.440)	27.14 (12.582)
Median (Minimum [Min.]-Maximum [Max.])	24.00 (14.0-85.0)	25.00 (13.0-98.0)
LS Mean	26.73	27.12
Treatment comparison		
Topical Diclofenac +Heat Patch versus (vs.) Topical Diclofenac +Placebo Patch		
Difference		-0.39
95% CI		-1.86, 1.08
p-value		0.8056

Table 2: Pain (score on a scale) following stair climbing on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of topical diclofenac plus a placebo patch

Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch
n	68	65
Mean (SD)	1.68 (0.984)	1.78 (1.053)
Median (Min.-Max.)	2.00 (0.0-4.0)	2.00 (0.0-4.0)
LS Mean	1.67	1.74
Treatment comparison		
Topical Diclofenac + Heat Patch vs. Topical Diclofenac + Placebo Patch		
Difference		-0.07
95% CI		-0.32, 0.18
p-value		0.7895

Secondary Outcome Results (ITT population N=69):

Table 3: Time (seconds) to climb stairs on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of placebo gel plus a heat patch

Treatments	Topical Diclofenac+ Heat Patch	Placebo Gel+ Heat Patch
n	68	65
Mean (SD)	26.82 (11.440)	27.69 (12.180)
Median (Min.-Max.)	24.00 (14.0- 85.0)	24.00 (13.0-80.0)
LS Mean	26.73	27.80
Treatment comparison		
Topical Diclofenac + Heat Patch vs. Placebo Gel + Heat Patch		
Difference		-1.07
95% CI		-2.44, 0.31
p-value		0.1520

Table 4: Pain (score on a scale) following stair climbing on 72 hrs treatment of topical diclofenac plus a heat patch with 72 hrs treatment of placebo gel plus a heat patch

Treatments	Topical Diclofenac+ Heat Patch	Placebo Gel+ Heat Patch
n	68	65
Mean (SD)	1.68 (0.984)	1.78 (1.008)
Median (Min.-Max.)	2.00 (0.0-4.0)	2.00 (0.0-4.0)
LS Mean	1.67	1.74
Treatment comparison		
Topical Diclofenac + Heat Patch vs. Placebo Gel + Heat Patch		
Difference		-0.07
95% CI		-0.31, 0.17
p-value		0.7231

Table 5: Time (seconds) to walk 20 m on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	65
Mean (SD)	18.78 (6.279)	18.83 (6.501)	19.57 (7.351)
Median (Min.-Max.)	18.00 (12.0-58.0)	18.00 (12.0-53.0)	18.00 (12.0-61.0)
LS Mean	18.72	18.93	19.69
Treatment comparison			
Topical Diclofenac + Heat Patch vs. Topical Diclofenac + Placebo Patch			
Difference	-0.22		
95% CI	-1.03, 0.59		
p-value	0.7697		
Topical Diclofenac + Heat Patch vs. Placebo Gel + Heat Patch			
Difference	-0.98		
95% CI	-1.78, -0.17		
p-value	0.0142		
Table 6: Time (seconds) to walk 40 m on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	65
Mean (SD)	38.57 (12.760)	38.09 (11.051)	39.91 (14.345)
Median (Min.-Max.)	36.50 (21.0- 118.0)	36.00 (25.0- 102.0)	38.00 (25.0- 116.0)
LS Mean	38.45	38.35	40.23
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.10		
95% CI	-1.28, 1.49		
p-value	0.9796		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-1.78		
95% CI	-3.17, -0.40		
p-value	0.0087		
Table 7: Pain following walking 40 m on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	65
Mean (SD)	1.10 (1.010)	1.17 (1.039)	1.26 (1.079)
Median (Min.-Max.)	1.00 (0.0- 4.0)	1.00 (0.0- 4.0)	1.00 (0.0- 4.0)
LS Mean	1.09	1.12	1.22
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.03		
95% CI	-0.29, 0.22		
p-value	0.9451		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.13		
95% CI	-0.38, 0.13		
p-value	0.4276		

Table 8: Pain at rest on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	65
Mean (SD)	0.59 (0.833)	0.89 (0.954)	0.89 (1.002)
Median (Min.-Max.)	0.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	0.58	0.87	0.87
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.28		
95% CI	-0.53, -0.04		
p-value	0.0185		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.28		
95% CI	-0.53, -0.04		
p-value	0.0176		
Table 9: WOMAC scores on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch			
1. Pain Walking On Flat Surface			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	64
Mean (SD)	1.32 (0.905)	1.43 (0.829)	1.38 (0.917)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	1.33	1.39	1.33
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.06		
95% CI	-0.24, 0.12		
p-value	0.6627		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	0.00		
95% CI	-0.18, 0.17		
p-value	0.9980		
2. Pain Going Up Or Down Stairs			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	66	65	64
Mean (SD)	1.89 (0.862)	2.02 (0.780)	1.97 (0.890)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.89	2.00	1.95
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.10		
95% CI	-0.36, 0.15		
p-value	0.5709		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.06		
95% CI	-0.32, 0.20		
p-value	0.8248		
3. Pain That Disturbs Your Sleep			

Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	64
Mean (SD)	1.19 (1.011)	1.45 (0.867)	1.34 (0.996)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-4.0)
LS Mean	1.19	1.41	1.27
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.22		
95% CI	-0.44, -0.01		
p-value	0.0376		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.09		
95% CI	-0.30, 0.12		
p-value	0.5513		
4. Pain Sitting Or Lying			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	64
Mean (SD)	1.25 (0.904)	1.37 (0.928)	1.23 (0.850)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	1.25	1.35	1.21
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.10		
95% CI	-0.32, 0.12		
p-value	0.4705		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	0.04		
95% CI	-0.18, 0.26		
p-value	0.8935		
5. Pain Standing Upright			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	63
Mean (SD)	1.43 (0.869)	1.45 (0.771)	1.46 (0.981)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	1.42	1.43	1.42
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.00		
95% CI	-0.20, 0.20		
p-value	0.9989		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	0.00		
95% CI	-0.20, 0.20		
p-value	0.9991		
6. Severity of Stiffness after awake			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	65	63	61
Mean (SD)	1.60 (0.949)	1.65 (0.883)	1.67 (0.944)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.61	1.66	1.67
Treatment comparison			

Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference			-0.05
95% CI			-0.27, 0.16
p-value			0.8015
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference			-0.06
95% CI			-0.28, 0.16
p-value			0.7552
7. Severity Of Stiffness Later In Day			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	65	62	61
Mean (SD)	1.58 (0.768)	1.61 (0.817)	1.54 (0.886)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-3.0)
LS Mean	1.61	1.61	1.55
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference			0.01
95% CI			-0.20, 0.21
p-value			0.9970
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference			0.06
95% CI			-0.15, 0.27
p-value			0.7320
8. Difficulty In Descending Stairs			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	67	63	64
Mean (SD)	2.01 (0.945)	2.05 (0.851)	2.02 (0.882)
Median (Min.-Max.)	2.00 (0.0-4.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	2.02	2.03	2.02
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference			-0.01
95% CI			-0.26, 0.24
p-value			0.9974
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference			0.00
95% CI			-0.25, 0.25
p-value			0.9999
9. Difficulty In Ascending Stairs			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	67	62	64
Mean (SD)	1.96 (0.928)	2.13 (0.799)	2.00 (0.836)
Median (Min.-Max.)	2.00 (0.0-4.0)	2.00 (0.0-3.0)	2.00 (0.0-3.0)
LS Mean	1.95	2.12	1.99
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference			-0.16
95% CI			-0.39, 0.07
p-value			0.1946
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference			-0.04
95% CI			-0.26, 0.19

p-value	0.9039		
10. Difficulty In Rising From Sitting			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	67	63	64
Mean (SD)	1.63 (0.902)	1.62 (0.812)	1.67 (0.944)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.64	1.61	1.67
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.03		
95% CI	-0.19, 0.24		
p-value	0.9492		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.03		
95% CI	-0.24, 0.18		
p-value	0.9291		
11. Difficulty In Standing			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	67	63	64
Mean (SD)	1.39 (0.920)	1.43 (0.817)	1.45 (0.942)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	1.40	1.43	1.45
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.03		
95% CI	-0.22, 0.17		
p-value	0.9288		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.04		
95% CI	-0.24, 0.15		
p-value	0.8300		
12. Difficulty In Bending To Floor			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	67	63	64
Mean (SD)	1.91 (0.917)	1.97 (0.967)	1.91 (0.868)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-4.0)	2.00 (0.0-3.0)
LS Mean	1.92	1.95	1.90
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.03		
95% CI	-0.23, 0.18		
p-value	0.9338		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	0.03		
95% CI	-0.18, 0.23		
p-value	0.9448		
13. Difficulty Walking On Flat Surface			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	67	63	64
Mean (SD)	1.33 (0.927)	1.37 (0.867)	1.36 (0.949)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-4.0)

LS Mean	1.34	1.35	1.33
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.00		
95% CI	-0.20, 0.20		
p-value	0.9992		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	0.01		
95% CI	-0.18, 0.21		
p-value	0.9855		
14. Difficulty In Getting In/Out Of Car			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	64	64	65
Mean (SD)	1.77 (0.868)	1.84 (0.801)	1.82 (0.917)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.77	1.83	1.80
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.06		
95% CI	-0.26, 0.15		
p-value	0.7703		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.03		
95% CI	-0.23, 0.17		
p-value	0.9257		
15. Difficulty In Going Shopping			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	61	62	63
Mean (SD)	1.54 (0.867)	1.73 (0.813)	1.63 (1.036)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.57	1.67	1.61
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.10		
95% CI	-0.31, 0.11		
p-value	0.4716		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.04		
95% CI	-0.25, 0.17		
p-value	0.8916		
16. Difficulty In Putting Socks/Tights			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	64	63	64
Mean (SD)	1.52 (0.943)	1.54 (0.895)	1.53 (0.908)
Median (Min.-Max.)	1.00 (0.0-3.0)	2.00 (0.0-3.0)	1.00 (0.0-4.0)
LS Mean	1.52	1.51	1.52
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.00		
95% CI	-0.19, 0.20		
p-value	0.9977		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			

Difference	0.00		
95% CI	-0.20, 0.19		
p-value	0.9992		
17. Difficulty In Rising From Bed			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	64	64	65
Mean (SD)	1.53 (1.023)	1.56 (0.924)	1.58 (0.983)
Median (Min.-Max.)	1.50 (0.0-4.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.53	1.52	1.57
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.01		
95% CI	-0.22, 0.24		
p-value	0.9935		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.04		
95% CI	-0.27, 0.18		
p-value	0.8673		
18. Difficulty in taking off socks			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	63	63	64
Mean (SD)	1.52 (0.965)	1.48 (0.965)	1.53 (0.959)
Median (Min.-Max.)	1.00 (0.0-3.0)	2.00 (0.0-3.0)	1.50 (0.0-4.0)
LS Mean	1.52	1.47	1.53
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	0.05		
95% CI	-0.15, 0.25		
p-value	0.7927		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.01		
95% CI	-0.20, 0.19		
p-value	0.9924		
19. Difficulty In Lying In Bed			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	64	64	65
Mean (SD)	1.16 (0.912)	1.31 (0.924)	1.31 (0.983)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	1.16	1.26	1.27
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.10		
95% CI	-0.30, 0.10		
p-value	0.4287		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.11		
95% CI	-0.31, 0.09		
p-value	0.3519		
20. Difficulty In Getting In/Out Of Bath			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	57	54	53

Mean (SD)	1.89 (0.976)	2.02 (0.921)	1.87 (1.057)
Median (Min.-Max.)	2.00 (0.0-4.0)	2.00 (0.0-4.0)	2.00 (0.0-4.0)
LS Mean	1.93	2.04	1.88
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.11		
95% CI	-0.33, 0.11		
p-value	0.4257		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	0.04		
95% CI	-0.18, 0.26		
p-value	0.8759		
21. Difficulty In Sitting			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	64	63
Mean (SD)	1.25 (0.870)	1.36 (0.897)	1.32 (0.981)
Median (Min.-Max.)	1.00 (0.0-3.0)	1.00 (0.0-3.0)	1.00 (0.0-4.0)
LS Mean	1.26	1.34	1.30
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.09		
95% CI	-0.26, 0.09		
p-value	0.4395		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.05		
95% CI	-0.23, 0.13		
p-value	0.7605		
22. Difficulty In Getting On/Off Toilet			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	63
Mean (SD)	1.47 (0.889)	1.55 (0.830)	1.59 (0.927)
Median (Min.-Max.)	1.50 (0.0-3.0)	2.00 (0.0-3.0)	2.00 (0.0-4.0)
LS Mean	1.47	1.54	1.59
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.07		
95% CI	-0.27, 0.14		
p-value	0.6733		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.11		
95% CI	-0.32, 0.09		
p-value	0.3646		
23. Difficulty In Heavy Domestic Duty			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	64	64	63
Mean (SD)	2.14 (0.814)	2.30 (0.749)	2.19 (0.895)
Median (Min.-Max.)	2.00 (0.0-3.0)	2.00 (1.0-3.0)	2.00 (0.0-4.0)
LS Mean	2.18	2.26	2.19
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.08		
95% CI	-0.27, 0.10		

p-value	0.5031		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.01		
95% CI	-0.20, 0.18		
p-value	0.9948		
24. Difficulty In Light Domestic Duty			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	64
Mean (SD)	1.34 (0.874)	1.46 (0.772)	1.48 (0.854)
Median (Min.-Max.)	1.00 (0.0-3.0)	2.00 (0.0-3.0)	1.00 (0.0-3.0)
LS Mean	1.34	1.43	1.46
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.08		
95% CI	-0.29, 0.13		
p-value	0.5741		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.12		
95% CI	-0.33, 0.09		
p-value	0.3483		
Table 10: Mean consumption of rescue medication based on consumption per patient per treatment on treatment of topical diclofenac plus heat patch with topical diclofenac plus placebo patch and to placebo gel plus heat patch			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
n	68	65	65
Mean (SD)	3.82 (5.148)	4.12 (4.897)	4.37 (7.331)
Median (Min.-Max.)	0.00 (0.0- 16.0)	2.00 (0.0- 16.0)	0.00 (0.0- 48.0)
LS Mean	3.86	3.93	4.30
Treatment comparison			
Topical Diclofenac +Heat Patch vs. Topical Diclofenac+ Placebo Patch			
Difference	-0.07		
95% CI	-1.37, 1.23		
p-value	0.9889		
Topical Diclofenac +Heat Patch vs. Placebo Gel+ Heat Patch			
Difference	-0.44		
95% CI	-1.73, 0.86		
p-value	0.6697		
Safety Results (Safety population, N=69):			
Table 11: Number of Subjects With Treatment Emergent Adverse Events (AEs)			
Treatments	Topical Diclofenac+ Heat Patch	Topical Diclofenac+ Placebo Patch	Placebo Gel+ Heat Patch
N	68	65	65
Number of subjects with at least one AE, n (%)	5 (7.4)	14 (21.5)	11 (16.9)
Musculoskeletal And Connective Tissue Disorders			
Joint Swelling	0	3 (4.6)	2 (3.1)
Osteoarthritis	0	1 (1.5)	1 (1.5)
Arthralgia	0	1 (1.5)	0
Back Pain	0	1 (1.5)	0
Groin Pain	0	0	1 (1.5)
Pain In Extremity	0	0	1 (1.5)

Infections And Infestations			
Upper Respiratory Tract Infection	1 (1.5)	1 (1.5)	1 (1.5)
Localised Infection	0	1 (1.5)	1 (1.5)
Skin And Subcutaneous Tissue Disorders			
Erythema	2 (2.9)	0	0
Pruritus	0	0	2 (3.1)
Skin Induration	0	1 (1.5)	0
Gastrointestinal Disorders			
Nausea	1 (1.5)	1 (1.5)	0
Diarrhoea	1 (1.5)	0	0
Dyspepsia	0	0	1 (1.5)
General Disorders And Administration Site Conditions			
Fatigue	0	2 (3.1)	0
Discomfort	0	1 (1.5)	0
Feeling Hot	0	1 (1.5)	0
Nervous System Disorders			
Headache	0	2 (3.1)	1 (1.5)
Dizziness	0	0	1 (1.5)
Respiratory, Thoracic And Mediastinal Disorders			
Oropharyngeal Pain	0	0	1 (1.5)
Vascular Disorders			
Hypertension	1 (1.5)	0	0
Serious Adverse Events (SAEs) - On-Therapy			
No SAE was reported.			